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High-Frequency Somatosensory Thalamocortical Oscillations and Psychopathology in Schizophrenia

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Key Words
Somatosensory evoked potentials · Schizophrenia · High-frequency oscillations · Dipole source analysis · Thalamus dysfunction · Thought disorder · Delusions

Abstract
Human cortical somatosensory evoked potentials (SEPs), which are presumably generated in afferent thalamocortical and early cortical fibers, reveal a burst of superimposed early (N20) high-frequency oscillations (HFOs), around 600 Hz. There is increasing evidence of an imbalance of thalamocortical systems in schizophrenic patients. In order to assess correlations between somatosensory evoked oscillations and symptoms of schizophrenia, we investigated median nerve SEPs in 20 inpatients and their age-matched and gender-matched healthy controls using a multichannel EEG. Dipole source analysis and wavelet transformation were performed before and after application of a 450-Hz high-pass filter. In schizophrenics, the maximum HFOs occurred with a significantly prolonged latency. There was also a higher amplitude (energy) in the low-frequency range of the N20 component compared with the controls. Importantly, amplitudes (energy) of HFOs were inversely correlated with symptoms of formal thought disorder and delusions. Alterations of the thalamocortical somatosensory signal processing in schizophrenia with absence of an early HFO – assumed to be of inhibitory nature – could indicate a dysfunctional thalamic inhibition with increased amplitudes of N20, paralleled by enhanced positive schizophrenic symptoms.

Introduction

The central anatomic position and extensive cortical interconnectivity of the thalamus, and its regulatory 'gating' function for the input of most of the sensory systems have contributed to the concept of thalamic generator of the brain [1–3]. Thalamic dysfunction is regarded as a part of large-scale filter failure in the pathogenesis of psychotic diseases [4]. In schizophrenia, earlier hypotheses of a filter deficit for sensory information [5, 6] were extended when neuropsychological findings pointed in-

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creasingly to dysfunctional cortico-striato-thalamic connections [7, 8]. Recent studies on information processing deficits in schizophrenia [9, 10] strongly suggest a relationship with abnormal thalamocortical connections, in particular with prefrontal and temporolimbic areas. Thalamic alterations in schizophrenia were widely demonstrated anatomically [11–19] and metabolically [16, 20–24], though with nonuniform results.

Neurophysiologically, the central role of the thalamus in the regulation of cognitive and sensory cortical input is mainly supported by alterations of preattentive sensory gating in schizophrenic patients, predominantly demonstrated by a loss of inhibitory function as indicated by a deficient prepulse inhibition [2, 25, 26]. Still, electrophysiological studies – accurate in measurements of the time between stimulus and response – of possible thalamocortical dysfunctions in schizophrenia other than the startle response are rare. Previously, the variability of wave shapes of somatosensory evoked potentials (SEPs) in chronic schizophrenics was described as a high early and low late stability of amplitudes [27, 28] probably depending on the acuity of the disease. Jones and Miller [29] tried to establish latency differences of SEPs between schizophrenics and healthy controls as a measure of intrahemispheric transfer, but these findings were not shown to be replicable [30]. Nevertheless, by studying SEPs, nowadays the more detailed information on underlying physiological processes, derived from animal studies, can be related to modern noninvasive studies of somatosensory functioning in humans.

Human median nerve SEPs provide the possibility of investigating thalamocortical and early cortical processing more intensely by means of advanced analysis filtering tools [31]: SEPs of the median nerve when digitally high-pass filtered show a brief oscillatory burst with low amplitudes (<500 nV) and high frequency (600 Hz). These high-frequency oscillations (HFOs) are superimposed on the primary cortical low-frequency response represented by a parietal negativity peak component approximately 20 ms after stimulation, i.e., the N20 [32]. According to Allison et al. [33], the primary N20 component is mainly generated by excitatory postsynaptic potentials in the proximal segments of apical dendrites of pyramidal cells in Brodman area 3b. On the other hand, various cellular sites have been considered responsible for the HFOs, namely the thalamus and/or thalamocortical afferents [34], intracortical pyramidal cells [35] or postsynaptic axons [36], and, lately, inhibitory interneurons [37]. One generator for the HFOs was localized by means of magnetoencephalography near the N20 source in the hand area 3b [26, 38], possibly reflecting presynaptic repetitive discharges that were conducted in the terminal segments of thalamocortical axons and/or postsynaptic segments derived from neocortical neurons.

In association with multichannel EEG studies, dipole source analysis – a modern noninvasive method that allows localization of the main neuronal generators in the cortex by estimating intracerebral sources for surface scalp-recorded waveforms [39] – made it possible to demonstrate HFOs originating close to the thalamus [40, 41]. This source is assumed to be generated in the deep axon segments of thalamocortical fibers as it was most active between the brain stem (P14) and cortical sources (N20). Presynaptic activity, arriving at the sensorimotor cortex, was thought to originate, at least partially, in the deep axon segments of thalamocortical fibers. This source was also detected by invasive recordings in primates and humans [34, 42, 43]. Further intrathalamic SEP recordings in patients have confirmed a local high-frequency activity superimposed on the thalamic P16 [44].

At present, these two evoked somatosensory responses, N20 (low frequency) and 600 Hz (high frequency), have been shown to be independent components of SEPs: they can be dissociated functionally by variation of stimulus intensities [45], stimulus rates [41], double pulse stimulation [44], vigilance states [32, 46, 47], and by interference with different somatosensory stimuli [38] or motor tasks [48]. Thus, the 'SEP gating' of HFOs is thought to reflect timing processes of repetitive cerebral population spikes with regular amplitude recruitment [49] occurring for all components independent of, for example, the motor task.

In order to further investigate thalamic dysregulation as a pathophysiological factor in schizophrenia, an abnormal pattern of assumed thalamocortical HFOs should be present in these patients. The principal aim of this investigation was to test the hypothesis of thalamocortically generated SEP alterations in schizophrenic patients by a noninvasive electrophysiological study with multichannel EEG, followed by an analysis of low-frequency oscillations and HFOs, in relationship to the severity of symptoms.

Methods and Materials

Subjects

Twenty right-handed inpatients with schizophrenia (5 females, 15 males) were recruited at the Psychiatry Department of the University Hospital of Aachen, Germany. They all met the Axis I diagnoses for schizophrenia according to the DSM-IV criteria [50], con-

firmed by a detailed clinical interview and review of hospital records.

The mean age of the schizophrenic patients was 30.30 years (SD 9.33) with a range of 18–48 years. The mean age at illness onset was 25.80 years (SD 8.76), and the mean duration of illness since first onset was 4.45 years (median 3.00, SD 4.90) with an average episode number of 2.38 (SD 1.60), including 7 chronic patients with no full remissions. The average length of inpatient hospital stay at the time of the investigation was 56.72 days (median 36, SD 35.63). Before entering the study, the patients were screened for severe somatic illnesses. Psychiatric exclusion criteria were comorbidity with a major depressive episode and other affective disorders, current (<3 months) substance-related disorders, and all cognitive and mental disorders due to a medical condition. Seven patients revealed a past history of alcohol or substance abuse or dependence.

An age-matched and gender-matched control group was selected from the hospital staff members, medical, and other university students without any current or past psychiatric history, or major somatic illnesses. The mean age of controls was 31.11 years (SD 8.63). The patient group and control group did not differ in their age distributions.

After being orally informed of all details of the study, all participants gave their informed consent. Patients were tested during a stable period of their hospitalization.

Medication Status

All patients were treated with antipsychotic medications; 16 patients received atypical antipsychotic drugs (clozapine, olanzapine, amisulpride, risperidone), and 4 patients were treated with a typical antipsychotic agents (fluphenazine, flupentixol, perazine). The chlorpromazine-equivalent dosage of antipsychotics was 869.97 mg per day (SD 472.91 mg).

Clinical Symptom Assessment

The symptomatology of all patients was assessed based on clinician-rated instruments by an experienced senior psychiatrist who was blinded to the results.

The 18-item Brief Psychiatric Rating Scale (BPRS) [51] was administered, including the total score and the 5 subscales (anxiety-depression, anergia, thinking disturbance, hostility-suspiciousness, withdrawal-retardation). Furthermore, the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) [52, 53] were utilized. The SAPS contains 34 positive symptoms, whereas the SANS consists of 25 ratings of negative symptoms in schizophrenia. The scale of each symptom ranges from 0 (absent) to 5 (severe). The scores are compressed to 4 major positive and 5 major negative symptom scores, leading to a global positive and a global negative score. The global positive score contains the symptom clusters: hallucinations, delusions, bizarre behavior, and positive thought disorder. The global negative score contains the symptom clusters: affective flatness, anhedonia-asociality, avolition-apathy, alogia, and attentional impairment.

SEP Recording

All subjects were lying in a comfortable supine position in a sound-attenuated dark room that was electrically shielded. They were instructed to relax, remain motionless, with their eyes open. Electrical transcutaneous stimulation was performed with two electrodes over the median nerves on the wrists of the right and left hands consecutively. Single constant-current square wave pulses of a duration of 0.2 s were delivered with an intensity of twice the motor threshold on the opponens pollicis muscle and a stimulus rate of 6 Hz. Additionally, the subjects were instructed to silently count randomly presented 1-kHz tones and to recall the number of counts after each run of SEPs in order to preserve a stable level of vigilance. Error rates in healthy subjects were less than 5%, while the patient group performed with an error rate of less than 10%.

By using a 32-channel extended version of the 10/20-system channel EEG, we obtained SEP recordings from Ag^+/Cl^- scalp electrodes. C_z served as a reference. The impedance was kept below 5 kΩ. Beforehand, three-dimensional electrode positions, in each individual, were determined with a three-dimensional digitizer (ZEBRIS®). The A/D rate of the amplifiers (NeuroScan®) was set at 5 kHz, and the signals were band-pass filtered between 1 and 1,500 Hz (12 dB). Because of artifacts due to eye movements in the range of ± 100 μV, peaks above 100 μV at any scalp electrode were rejected for averaging procedures.

Data Analysis

Source Reconstruction Analysis

Finally, 4,000 artifact-free sweeps per side of stimulation were included in the analysis. Each sweep contained 500 addresses over a period of 100 ms, from 50 ms before to 50 ms after the stimulation. Source reconstruction was performed individually for each subject with dipole source analysis applying the Brain Electrical Source Analysis (BESA 3.0: MEGIS, Munich, Germany) software to the resulting files: the averaged waveforms were digitally filtered by a low-pass filter of 750 Hz (24 dB/octave slope, zero phase shift) and a high-pass filter of 20 Hz (12 dB/octave slope, forward filter). In order to reduce the data to a single waveform weighted on the activity of the neuronal generators of the SEPs, single dipole sources were fitted for each subject and each side for a time period between 14 and 25 ms. To adjust the individual data for average head geometry and conductivities, a spherical three-shell (scalp, skull, brain) head model was used with the assumptions of a scalp thickness of 6 mm (0.33 [1/(Ωm)]), a skull thickness of 7 mm (0.0042 [1/(Ωm)]), and a brain conductivity of 0.33 [1/(Ωm)] (fig. 1).

A single dipole is not an appropriate model for the early SEPs, and to model all the different early SEPs, a more complex source configuration with at least three dipoles is needed (for an explanation, see Buchner et al. [31]). The approach, chosen with one dipole based on the limitations of the investigated patient group, produced a unique solution and was considered to be sufficient to demonstrate differences in signal composition between the subgroups.

Time Frequency Analysis

Dipole parameters were exported to Matlab® (The MathWorks GmbH). For time frequency analysis of the source, a wavelet analysis was computed using the time-frequency toolbox of the Rice University (USA) resulting in a Morlet deconvolution. The program computes a scalogram, a diagram based on three axes, displaying components of frequency and energy at each time point. The frequency with the highest energy and its corresponding time point is detected automatically. In a first step, the frequency band between 40 and 450 Hz was analyzed: the frequency with the highest energy and its time point were determined within the range of the N20, followed by the same analysis procedures of the frequency band between 450 and 800 Hz. The resulting values were analyzed statistically.

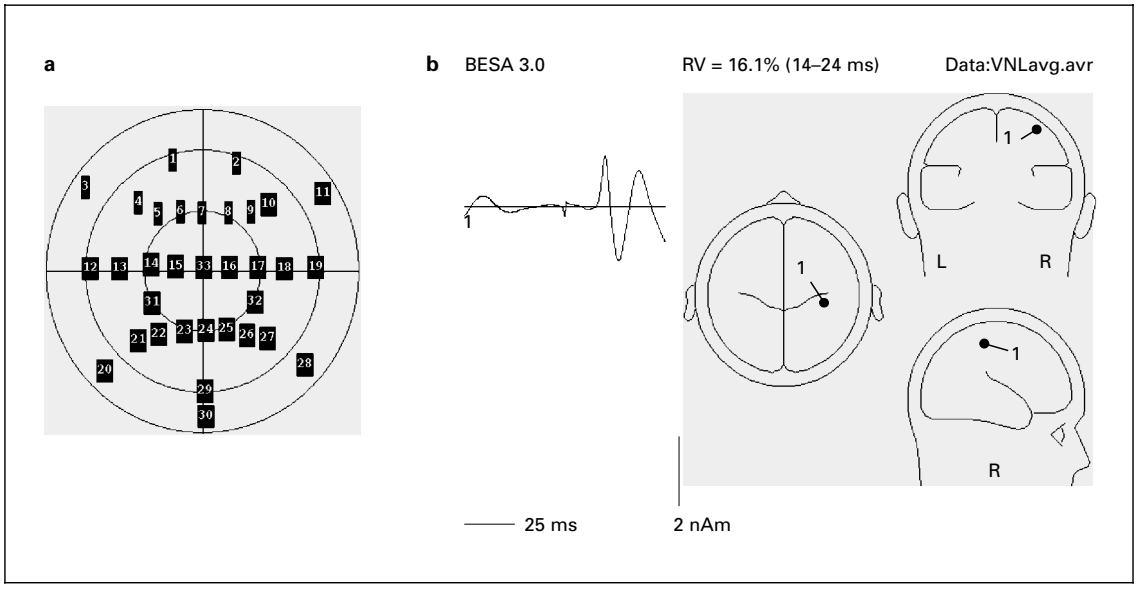

Fig. 1. 32-channel montage (**a**) and N20 dipole source activity and source model for the grand average of all subjects (**b**).

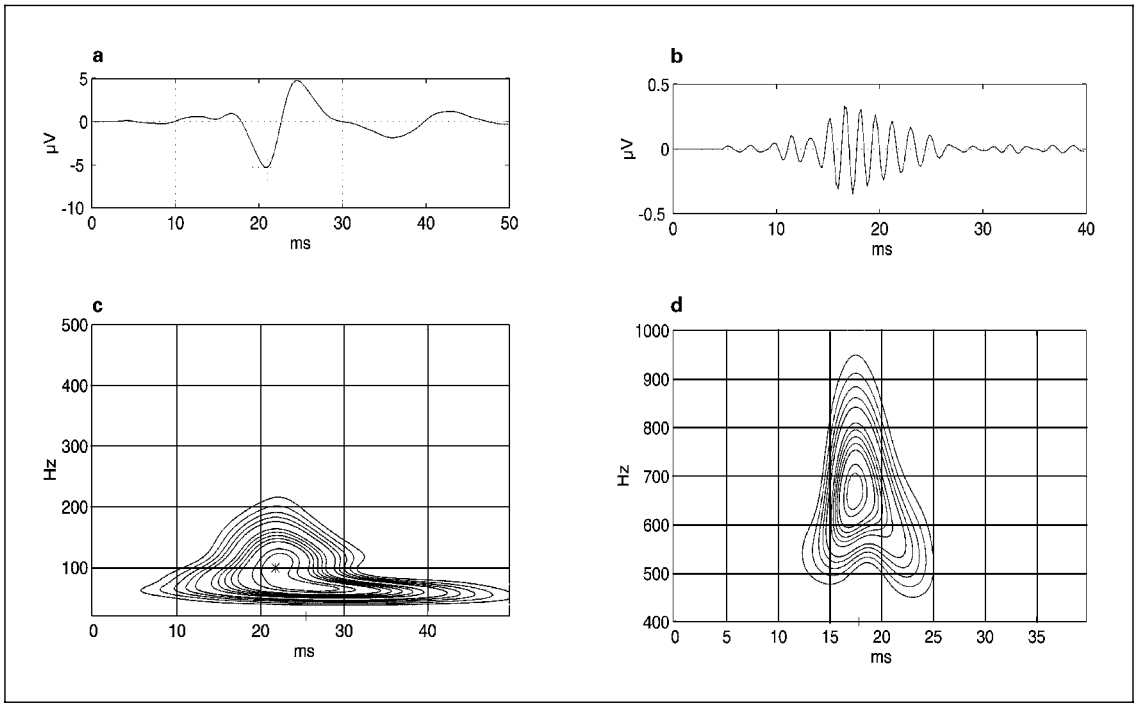

Fig. 2. Source waveform (**a**, **b**) and scalograms (**c**, **d**) of wave transformation analysis with the time point of highest energy level in the low-frequency, 40–450 Hz (**c**), and in the high-frequency, 450– 850 Hz (**d**) range of schizophrenic subjects.

Statistical Analysis

The two-tailed t test was applied for group differences between electrophysiological parameters (amplitude, latency, frequency). Correlation coefficients for variables of SEPs and clinical psychopathological scores were calculated by Spearman's nonparametric rank method, taking into account power analysis for the strength of the group ($\alpha = 0.5$, $\beta = 0.80$). In order to investigate the severity of disease symptoms, the median of the duration of illness served as a cutoff for two groups of subjects with longer and shorter time since onset of the first episode, followed by one-tailed t tests. Results were considered significant at $p < 0.05$. The SAS 8.0 package was used for all statistical analyses.

Results

SEPs/Electrophysiological Parameters

Comparing the sides of stimulation within each group, there were no significant differences between the frequency ranges for left and right hands. Therefore, the data of left and right hand stimulation were combined for further analysis. This led to a subsequent comparison of 20 data sets per group. Low- and high-frequency ranges were analyzed subsequently (fig. 2). The two-tailed t test was performed for latencies, amplitudes, and frequencies of the peaking points in the three-dimensional scalogram.

In all patients and controls, low- and high-frequency (600 Hz) SEP components were observed. For both frequency ranges, significant differences between the groups of schizophrenic patients and normal controls were found.

(1) Low-frequency range (40–450 Hz): the energy (amplitude) of the low-frequency maximum was significantly higher in the schizophrenic patients compared with the healthy controls (d.f. = 38, t = –2.14, p = 0.039). Latencies and frequencies did not differ significantly between the groups (table 1).

(2) High-frequency range (450–850 Hz): the latency of the maximum of high-frequency activity as detected by Morlet transformation was significantly delayed in the group of schizophrenic patients (d.f. = 38, t = –2.05, p = 0.048). Frequencies and energies did not differ significantly (table 1).

Clinical Pathopsychological Findings

Mean values, median values, standard deviations, and ranges of the results of the assessment of positive (SAPS) and negative (SANS) symptoms as well as global psychiatric (BPRS) symptoms in all schizophrenic patients are presented in table 2.

Table 1. Mean values (including SD in parentheses) of median nerve SEPs in schizophrenic patients (n = 20) and healthy controls (n = 20)

SEPs	Schizophrenics	Controls	p
N20			
Latency, ms	20.70 (1.30)	21.08 (2.13)	ns
Frequency, Hz	71.71 (12.23)	74.77 (17.88)	ns
Energy, μV^2	612.19 (230.51)	476.77 (163.55)	*
HFOs			
Latency, ms	19.33 (1.90)	17.98 (1.45)	*
Frequency, Hz	602.31 (33.53)	597.73 (47.15)	ns
Energy, μV^2	42.75 (12.39)	36.69 (14.24)	ns

* $p < 0.05$. ns = Nonsignificant.

Table 2. Mean and median values (including SD in parentheses) of scores for psychopathological symptoms in schizophrenic patients (n = 20)

Test	Mean (SD)	Median	Range
SAPS			
Total positive score	10.1 (3.5)	9.5	4–16
Hallucinations	1.4 (1.3)	1.0	0–4
Delusions	2.2 (1.1)	2.0	0–4
Bizarre behavior	2.2 (0.8)	2.0	1–4
Formal thought disorder	2.1 (0.9)	2.0	1–4
Inappropriate affect	2.3 (1.3)	2.0	0–4
SANS			
Total negative score	12.5 (4.3)	12.5	2–21
Affective flattening	2.2 (1.4)	2.0	0–4
Alogia	1.7 (1.2)	2.0	0–5
Avolition-apathy	2.9 (0.9)	3.0	1–4
Anhedonia-asociality	2.6 (0.9)	3.0	1–4
Attentional impairment	2.8 (1.0)	3.0	0–4
BPRS			
Total score	58.4 (12.3)	56.5	41–83
Anxiety-depression	13.2 (3.9)	13.0	5–21
Anergia	12.2 (3.7)	11.0	6–19
Thought disorder	12.35 (3.7)	13.0	5–18
Activation	11.4 (3.4)	11.0	5–17
Hostile-suspiciousness	9.4 (4.1)	9.0	3–19

SEPs and Clinical Relationships

The correlations between clinical psychopathological symptoms and HFOs are shown in table 3. There was a significant negative correlation between HFO amplitude and delusions (r = –0.51; p = 0.03), as well as between

Table 3. Correlation of clinical symptoms and the N20 measures of HFO (600 Hz) in schizophrenic patients (n = 20)

Test	Latency ms	Frequency Hz	Energy μV^2
SAPS			
Total positive score	0.10	–0.27	–0.37
Hallucinations	–0.24	–0.32	0.04
Delusions	0.19	–0.19	–0.50*
Bizarre behavior	–0.10	–0.04	–0.27
Formal thought disorder	0.20	–0.34	–0.51*
Inappropriate affect	0.28	0.09	–0.25
SANS			
Total negative score	0.31	0.29	–0.15
Affective flattening	0.29	0.35	–0.15
Alogia	0.07	0.08	–0.18
Avolition-apathy	0.47*	0.29	–0.11
Anhedonia-asociality	0.08	0.30	0.18
Attentional impairment	0.36	0.16	–0.26
BPRS			
Total			
Anxiety-depression	–0.37	–0.05	–0.02
Anergia	0.12	0.41*	–0.11
Thought disturbance	0.03	–0.33	–0.40*
Activation	–0.09	–0.22	–0.17
Hostile-suspiciousness	0.14	–0.12	–0.23

*$p < 0.05$, $\alpha = 0.05$, $\beta = 0.80$. Values are Spearman's correlation coefficients.

HFO amplitude and formal thought disorder (r = –0.51; p = 0.02). The latter was paralleled by a trend toward a negative correlation between HFO amplitude and formal thought disturbance in the BPRS (r = –0.40; p = 0.08). Concerning negative symptoms of schizophrenia, the latency of high-frequency SEP parameters was positively correlated with apathy (r = 0.47; p = 0.03) and there was a trend toward a correlation for HFO frequency and anergia (r = 0.41; p = 0.07) as well. However, a more detailed analysis of influences of medications on apathy or anergia did not show any positive correlation ($0.46 < p < 0.92$). Otherwise, there were no correlations for the low-frequency SEP parameters with clinical symptoms of schizophrenia.

SEPs and Medical History

Apart from a trend toward a correlation between neuroleptic dosage as measured by the chlorpromazine equivalent and the duration of illness (r = 0.46, p = 0.07), we did not note any significant influence of the medication on the electrophysiological SEP parameters, on age, onset or type of symptoms (data are not presented in detail). Moreover, there was a significant difference in the amount of neuroleptic dosage in the patients with a duration of schizophrenia of more than 2 years as compared with a group with a 2-year or shorter duration ($\chi^2 = 6.73$, d.f. = 1, p = 0.01). The duration of illness (median value) correlated positively with the frequency of N20 (r = –0.50, p = 0.04). There was also a trend toward a correlation between duration of illness and delusions (r = 0.46, p = 0.06).

Discussion

In this study of 20 schizophrenic patients and their age-matched and gender-matched controls, differences between low- and high-frequency components of median nerve evoked SEPs were registered with a 32-multichannel EEG, followed by advanced techniques with dipole source analysis and a wavelet transformation before and after high-pass filtering. The purpose of the investigation was to evaluate scalp surface EEG data of presumed intracranial thalamocortical somatosensory source in relationship to symptoms and severity of the disorder.

First, an augmentation in the mean amplitude of the low-frequency energy (around N20) was detected in schizophrenics, compared with healthy controls. This result of a higher amplitude of the early low frequency is in accordance with previous SEP studies in schizophrenia: the early part of SEPs in patients with chronic schizophrenia was found to be exceptionally stable and accentuated [27, 28]. These findings were interpreted as an impairment of thalamic filtering of the afferent sensory information to the cortex. The stimulus barrier was considered to be exceptionally weak in schizophrenics [28]. Remitted schizophrenics did not show any differences in latencies or amplitudes in an event-related study on SEPs [54], although attention-related reduced areas and prolonged latencies of the cognitive component N1 were observed.

The second finding of a significantly prolonged latency of the maximum HFO activity (600 Hz) in the group of schizophrenic patients is of interest because the HFOs presumably reflect time processing of rapidly repeating population spikes in thalamocortical afferences and the receiving neocortical cell populations [48]. Based on animal data, Jones et al. [37] ascribed the cause of cerebral high-frequency activity, obtained by single cell monitoring, to a possible epiphenomenon of inhibitory interneuronal activity. Furthermore, there is evidence for a pre-

synaptically and postsynaptically generated component of the HFOs [55]; the early presynaptic component is, most probably, generated by specific thalamocortical axonal terminals. So far, the cortically generated component of HFOs has been shown to be influenced by NMDA receptor antagonists [55] with possible effects on inhibitory GABA-ergic mechanisms, which is supported by the hypothesis that HFOs represent activity of GABA inhibitory interneurons responding to thalamocortical input [38]. Glutaminergic neurons are the major excitatory pathways linking the cortex, limbic systems, and thalamus, regions that have been implicated in schizophrenia, with dysfunctional glutaminergic and related dopaminergic neurotransmission [8, 56]. Consequently, under the assumption that the investigated HFOs are of inhibitory nature, the absence of early HFOs in the group of schizophrenics could point to a dysfunctional inhibition of thalamocortical and early cortical afferents in schizophrenia, resulting in higher cortical input of sensory information as expressed by enhanced amplitudes of the cortical low-frequency SEPs around N20.

Moreover, if the increase in HFO latency of the schizophrenic group reflects an impairment of thalamocortical somatosensory information processing, the thalamic reticular nucleus is probably involved. This nucleus selectively gates neurotransmission from the thalamus to the neocortex and continually regulates thalamocortical activity [1]. Furthermore, it is thought to be related to the control of vigilance and alertness as well as in the production of epileptic discharges [57, 58]. Across the sleep-wake cycle, somatosensory HFOs were found to be decreased in non-REM states at the level of thalamus and cortex but not at the brainstem, while the amplitude of the concomitant N20 was dissociated [32, 38, 47]. The reticular thalamic nucleus regulating arousal and vigilance supposedly represents one main candidate for modulation of HFOs [46].

In psychopathology, negative correlations of the HFO energy (amplitude) were seen with the positive symptom scale, in particular with positive thought disorder and delusions. Additionally, there was also a trend toward a negative correlation between HFO energy and thought disturbance in the broader and less disease-specific BPRS. Otherwise, patients with a long duration of illness showed more delusions and enhanced low early frequencies compared with the group with a shorter course of disease. This might point to a relationship between both formal thought disorder and delusional thinking with an altered thalamic function. In a positron emission tomography study, Siegel et al. [22] demonstrated an association between reduced thalamic activity and the occurrence of schizophrenic positive symptoms (e.g. the total BPRS score), though there were no group differences in the thalamic activity between schizophrenics and controls. Thalamic (and cortical) glucose metabolic rate, in particular in the anterior and mediodorsal nucleus, was also found to be reduced in another study with deficit schizophrenics as compared with nondeficit schizophrenics [16]. In both first-episode and chronic schizophrenics, a reduced blood flow in prefrontal areas and an enhanced blood flow in thalamic (and cerebellar) regions has been observed [24]. A disturbance of the integrity of the lateral fronto-thalamic-neocortical circuit may lead to sensory overstimulation, disorientation, and mnestic deficits with resulting severe psychological and cognitive deficits. This may also occur in patients with lesions of the dorsomedial nucleus or the bidirectional fibers connecting the thalamus and the frontal lobes [1, 59]. Our finding of a correlation between thought disorder and abnormal HFOs, assumed of thalamocortical origin, is also supported by findings in a rare case of a patient who presented with bilateral paramedian thalamic infarcts and subsequently decreased thalamic and basal ganglia blood flow: despite a characteristic diencephalic amnesia, she showed a bizarre, severely disordered, and at times incoherent speech in contrast to a relatively preserved lexical and morphosyntactic linguistic production; this finding was interpreted as a surface manifestation of a thought disorder [60].

In the past, a disturbance of thalamic filtering as a pathophysiological basis of positive symptoms in schizophrenia was postulated by Fish [5]. As early as 1911, Bleuler [61] had considered the 'loosening of associations' a fundamental core symptom of schizophrenia. At the time when this idea was somehow reconstituted as 'cognitive dysmetria', with disturbance of perception, encoding, retrieval, discrimination of information and prioritization of experiences [9], it was emphasized that the linkage in the breakdown of 'collective' thalamic components could represent the basis of fragmentation of thought processes as in schizophrenia [10]. Regular mechanisms of filtering and inhibiting irrelevant information at the thalamic level before it reaches the neocortex may have become dysfunctional. In this context, the absence of early HFOs could represent a dysfunctional thalamic inhibition with enhanced amplitudes of N20 and increased prevalence of positive schizophrenic symptoms of thought processes. Sensorimotor gating alterations as measured by prepulse inhibition [62] were also shown to correlate with disturbed thinking (Rohrschach test) and delusions (SAPS). Another EEG approach suggested that

cortical EEG alpha rhythm is correlated with alpha rhythm recorded from the thalamus and related thalamic neuronal activity expressed as glucose metabolic rate in humans [63]. However, this pattern was not observed in schizophrenics [64].

As negative symptoms may be induced by antipsychotic medications [65], inverse correlations between anergia (BPRS) and maximum frequency of HFOs may be explained by drug effects. There was also a positive correlation between avolition/apathy (SANS) and HFO latency. In some functional studies with schizophrenics, a correlation of negative symptoms or neuroleptic responsiveness with impaired thalamic perfusion was observed [66]. In our study, there was no correlation between the amount of the neuroleptic dosage (chlorpromazine equivalent) and psychopathological symptoms. The majority of schizophrenics were treated with atypical antipsychotics. Although Klostermann et al. [48] did not find any effects of anticonvulsants, they demonstrated a higher variability of both bursts and N20 in a mixed sample of epileptic patients compared with healthy controls. Patients with Parkinson's disease exhibited an increased early high-frequency component, while an augmented later burst component around 25–33 ms was found in patients with myoclonus epilepsy [67].

Our study has methodological limitations. First, the study size of our patient group was rather small. Since the investigation required some effort by the participants, we considered the number of investigated subjects to be sufficient, based on similar sample sizes in basic research [49]. Considering that the subjects chosen had to be patient and vigilant enough to go through the experimental session, the findings are not fully representative for the group of schizophrenics. Additionally, the number is not sufficient to effectively differentiate subgroups. Another implication is that some of the nonsignificant results may indeed be false-negative values.

Hence, a further limitation of the study is that all patients were taking antipsychotic drugs before and during the study. Previous results showed that single dosages of haloperidol were not affecting the amplitude of the early median nerve SEP in healthy individuals [68]. Although the effects of haloperidol in metabolic imaging studies of schizophrenics are contradictory [20, 21], a reduction of glucose metabolism in basal ganglia and thalamus was demonstrated after withdrawal of the drug [23]. Furthermore, regional blood flow abnormalities have not always been due to chronicity of illness or effects of medications [24]. Thalamic size may be increased by medications [15], although this finding has not been confirmed. Such effects were also shown for other subcortical structures [69]. Moreover, in the meta-analysis of comparable magnetic resonance imaging studies of Konick and Friedman [18], most of the patients presenting moderately smaller absolute and relative thalamic sizes compared with controls in the meta-analysis were medicated. Although the majority of our patients were treated with atypical antipsychotics, comparable data of effects of different types of antipsychotics on SEPs are not available. Only in animal studies, chronic treatment with clozapine and haloperidol was shown to change regulation of subcortical D_1 and D_2 dopaminergic receptors of the primary somatosensory cortex [70]. Still, our results of an increase in the low-frequency energy of the N20 signal is in accordance with the few available SEP investigations in neuroleptic-free schizophrenics [27]. Caution was also applied to the usage of benzodiazepines since lorazepam was found to increase the latency of HFOs and to decrease frequencies of N20 and HFOs in a magnetoencephalography study [71]. Thus, patients who needed benzodiazepines during the same hospitalization were excluded from this study.

Although caution is indicated when linking aberrant cortical oscillations with characteristic cognitive deficits resulting from a dysfunctional prefrontal-thalamic-cerebellar circuitry [9], HFOs might offer an understanding of the organization of sensory pathways in relation to perception and also put new insight into perceptual and cognitive deficits in schizophrenia. Fast thalamocortical oscillations and their associated intracellular events broaden the understanding of the classical picture of cellular processes underlying the evoked potential complex [37]. Still, the question as to whether electric alterations linked to thalamocortical dysfunction represent the cause or the consequence of positive schizophrenic symptoms remains unanswered, of course; yet HFOs should be considered a specific tool for investigation of abnormalities in somatosensory signal processing. These investigations should be conducted in schizophrenic subgroups.

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